2-GUANIDINYLIMIDAZOLIDINEDIONE COMPOUNDS AND METHODS OF MAKING AND USING THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 60/523,670, filed 21 Nov. 2003, listing Ai J. Lin, Quan Zhang, Jian Guan, and Wilbur K. Milhous as inventors, which is herein incorporated by reference in its entirety.

ACKNOWLEDGMENT OF GOVERNMENT SUPPORT

This invention was made by employees of the United States Army. The government has rights in the invention.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to 2-guanidinylimidazolidinedione compounds, methods of making and purifying 2-guanidinylimidazolidinedione compounds, and methods of using the 2-guanidinylimidazolidinedione compounds to prevent, treat, or inhibit malaria in a subject.

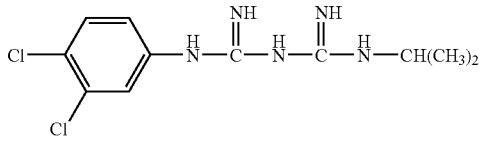
2. Description of the Related Art

The current global situation with respect to malaria indicates that about two billion people are exposed to the disease and of these 400 million people are already infected. See Trigg, P. I., and A. V. Kondrachine (1998) The Current Global Malaria Situation, Chapter 2, p. 11–22, in MALARIA PARASITE BIOLOGY, PATHOGENESIS AND PROTECTION. Ed. I. W. Sherman, ASM Press, Washington, D.C. Each year between 100 to 200 million new cases of infection are reported and

approximately 1 to 2 million people die due to malaria. The situation is rapidly worsening mainly due to non-availability of effective drugs and development of drug resistance of a large number of non-immune people in areas where malaria is frequently transmitted. See White, N.J. (1998) Br. Med. Bull. 54:703–715.

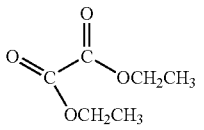
WR182393 is a mixture of cyclic dicarboxamide derivatives of chlorproguanil (1), the latter of which is highly active against primary exoerythrocytic forms of

(1)



Plasmodium falciparum and *P. vivax*. See Covell, G. et al. (1949) British Medical Journal 1:88–91; and Curd, F. S. H. et al. (1945) Annals of Tropical Medicine and Parasitology 39:208–216. The compound was synthesized first by Werbel et al. in 1972 and later by Starks Associates Co. by reacting chloroguanil (1) with diethyl oxalate (2)

(2)



according to the following Scheme 1:

Scheme 1